APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Tin
CAS Numbers: 7440-31-5
Date: April 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 0.3 [X] mg/kg/day [ ] ppm

Reference: De Groot AP, Feron VJ, Til HP. 1973. Short-term toxicity studies on some salts and oxides of tin in rats. Food Cosmet Toxicol 11:19-30.

Experimental design: The effect of stannous chloride was studied in male and female Wistar rats (10/sex/dose level) for 13 weeks at dietary levels of 0, 300, 1,000, 3,000, and 10,000 ppm. Using a conversion dietary factor of 0.05 kg food/kg body weight/day and the molecular weight of 118.69 for tin, it can be estimated that the diet provided approximate doses of 0, 9.5, 32, 95, or 315 mg Sn/kg/day. End points monitored included: survival, body weight, food intake, hematology (hemoglobin, hematocrit, total erythrocytes, total and differential leukocytes), serum chemistry (transaminases, alkaline phosphatase, bilirubin), urinalysis, organ weights (nine organs), and gross and microscopic pathology. Tin in the standard diet was not determined, but the concentrations of calcium, phosphorus, iron, copper, and zinc were known. The concentrations of these minerals were consistent with the concentrations in standard rat's diets, except for the amount of zinc, which was about 50% of that found in the standard diet.

Effect noted in study and corresponding doses: The highest dietary level (315 mg Sn/kg/day) caused reduced food consumption and abdominal distension on week 1. At week 8, loss of body weight occurred in males and females, and one male died. At week 9 another three males died and the group was discontinued. Rats in the 95 mg/kg/day level showed poor appetite and abdominal distension the first 2 weeks; this was associated with decreased food consumption, but they kept growing. At termination, no significant differences in body weights were seen. Food consumption was low also at 32 mg/kg/day, but only on week 1. Hemoglobin concentration was significantly reduced starting at week 4 at 95 and 315 mg/kg/day (about 12 and 20%, respectively) and only at week 4 in 32 mg/kg/day males (3% reduction). Terminal hemoglobin and hematocrit were significantly reduced only in high-dose males (6 and 4%, respectively). Tin had no noticeable effect on osmotic resistance of the erythrocytes or on the number of reticulocytes. Serum alkaline phosphatase was significantly decreased at termination in both sexes but there was no significant effect on transaminases or in bilirubin. Terminal urine samples were unremarkable, as were relative organ weights. Rats from the high-dose group which had to be terminated early showed distended intestines, slight edema of the pancreas, and grayish-brown livers. There was moderate testicular degeneration, severe pancreatic atrophy, spongy white matter in the brain, acute bronchopneumonia, enteritis and liver changes characterized by homogeneous appearance of the liver cell cytoplasm and mild proliferation of the bile duct epithelium. In the other groups at termination, treatment-related effects included bile duct epithelium proliferation and homogeneous cytoplasm at 95 mg/kg/day. The 95 mg/kg/day dose level is considered a minimal LOAEL based on the unknown biological significance of a transient 12% reduction in hemoglobin concentration.

Dose and end point used for MRL derivation: 32 mg/kg/day; decreased hemoglobin concentration.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Yes.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure?
No

Other additional studies or pertinent information that lend support to this MRL: The effects of the administration of stannous chloride, stannous orthophosphate, stannous sulfate, and stannous tartrate at the same dietary levels as above in the diet of rats for 4 weeks are in agreement with the data from the 13-week study (De Groot et al. 1973). The LOAELs for body weight gain, depressed hemoglobin and hematocrit values, and liver histopathology at 4 weeks were seen with the 3,000 ppm diet in males. The NOAEL was the 1,000 ppm diet. With the orthophosphate and tartrate salts, the differences in hemoglobin and hematocrit were not significant with the 3,000 ppm diet, but were significant with the 10,000 ppm diet.

Janssen et al. (1985) reported a LOAEL of 7.9 mg/kg/day for significant decreases in hemoglobin in rats fed a diet containing stannous chloride for 28 days. However, the standard diet contained only 20% of the copper reported for the diet in the De Groot et al. (1973) study. The lower concentrations of these minerals may have made the rats in the Jenssen et al. (1985) study more susceptible to the effects of tin on hematopoiesis. Transient hemolytic anemia was also reported in rabbits administered 10 mg tin/kg/day (as stannous chloride), the only dose level tested, by gavage for 4 months (Chmielnicka et al. 1993). However, no information was provided in that study regarding the trace mineral composition of the diet.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Dibutyltin dichloride
CAS Number: 683-18-1
Date: April 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 28
Species: Rat

Minimal Risk Level: 0.005 [X] mg/kg/day [ ] ppm

Reference: Seinen W, Vos JG, van Krieken R, et al. 1977b. Toxicity of organotin compounds. III. Suppression of thymus-dependent immunity in rats by di-n-butyltindichloride and di-n-octyltindichloride. Toxicol Appl Pharmacol 42:213-224.

Experimental design: Groups of male and female weanling Wistar rats (5–10/group) were fed diets containing 0, 50, or 150 ppm of the test material (>98% pure) for 4–6 weeks. Based on a body weight of 0.2 kg, it can be estimated that these levels provided doses of dibutyltin dichloride of approximately 0, 5, and 15 mg/kg/day (EPA 1988). End points examined included body weight and parameters of humoral and cellular immune responses. The humoral immune response was assessed by measuring formation of antibodies against SRBC and *E. coli* lipopolysaccharide. Rats were immunized intraperitoneally with SRBC 5 days before termination of the experiments. The cellular immune response was assessed by examining allograft rejection (rats were grafted at week 7).

Effects noted in study and corresponding doses: Final body weight after 4 weeks of exposure was not significantly altered relative to controls, but it was 28% lower than controls in the high-dose group after 6 weeks of exposure. Allograft rejection time was significantly delayed in the high-dose group relative to controls. In the tests for humoral response, the number of antibody-producing cells per million spleen cells was not affected, but the number per whole spleen was significantly decreased in a dose-related manner. This response was associated with a decreased hemagglutination titer in the high-dose group. The antibody titers against *E. coli* lipopolysaccharide were slightly but not significantly lower in treated groups than in controls. The dose of 5 mg/kg/day is the study LOAEL based on the reduction in hemagglutinating antibodies against SRBC.

Dose and end point used for MRL derivation: 5.0 mg/kg/day; immunological effects.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Yes. A food factor of 0.1 kg food/day/kg body weight was calculated using a body weight of 0.2 kg (from study) in an allometric equation (EPA 1988).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure?
No

Other additional studies or pertinent information that lend support to this MRL: Limited additional information was available for dibutyltin dichloride from intermediate-duration studies. Gaunt et al. (1968) conducted a 90-day dietary general toxicity and histopathology study in rats and found no significant effects other than a slight reduction in hemoglobin with the highest dose tested (5.7 mg/kg/day); no effect was seen at 3.4 mg/kg/day. Although the Gaunt et al. (1968) study defined a NOAEL and, possibly a minimal LOAEL, the immunological alterations reported in the Seinen et al. (1977b) study are preferred as basis for the intermediate-duration oral MRL because of the known immunotoxic properties of dibutyltins (i.e., Seinen et al. 1977a) and tributyltins (dibutyltin is a metabolite of tributyltin; Matsuda et al. 1993; Ueno et al. 1994). In two acute-duration oral studies in rats, serious LOAELs were described at or below the 5 mg/kg/day intermediate-duration LOAEL from Seinen et al. (1977b). In Ema et al. (1991b), 5 mg/kg/day was a serious developmental LOAEL and in Ema and Harazono (2000), 3.8 mg/kg/day was a serious reproductive LOAEL. However, in these two studies, the rats were treated with dibutyltin dichloride by gavage in oil, and the bolus administration may have contributed to the severity of the effects.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Tributyltin oxide
CAS Number: 56-35-9
Date: April 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 66
Species: Rat

Minimal Risk Level: 0.0003 [X] mg/kg/day [ ] ppm

Reference: Vos JG, De Klerk A, Krajnc EI, et al. 1990. Immunotoxicity of bis(tri-*n*-butyltin)oxide in the rat: effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young versus aged rats. Toxicol Appl Pharmacol 105:144-155.

Experimental design: Groups of male Wistar rats were fed a diet containing 0, 0.5, 5, or 50 ppm tributyltin oxide (95.3% pure) for 4.5–6 months. This diet provided approximately 0, 0.025, 0.25, and 2.5 mg/kg/day of the tin compound. Parameters of specific resistance evaluated included IgM and IgG response to ovalbumin and delayed-type hypersensitivity (DTH) response to ovalbumin and tuberculin after 6 months of treatment; resistance to *Trichinella spiralis* infection after 5.5 months; mitogenic response of thymus and spleen cells after 4.5 months; and surface marker analysis of mesenteric lymph nodes after 6 months. Parameters of nonspecific resistance examined included clearance of *Listeria monocytogenes* from the spleen after injection at 5 months and natural cell-mediated cytotoxicity of spleen and peritoneal cells after 4.5 months.

Effects noted in study and corresponding doses: Neither body weight nor spleen weight were significantly altered after 4.5 months of treatment, but thymus weight was reduced by 17% relative to controls in the high-dose group. Neither the IgM nor IgG response to ovalbumin and *T. spiralis* were altered after 5.5 months of exposure. The immunoglobulin E (IgE) responses to *T. spiralis*, as determined by the passive cutaneous anaphylaxis reaction, were suppressed in a dose-related manner (significant in the mid- and high-dose groups). The DTH reactions to ovalbumin and tuberculin were not significantly altered after 6 months of dosing. There was an increase in the number of larvae *T. spiralis* in muscle after infection in the mid- and high-dose groups after 5.5 months of exposure to the tin compound. No significant effect was observed on the response of spleen cells to T- and B-mitogens after 4.5 months. The cell surface marker analysis of mesenteric lymph node cells showed a reduction in the relative count of T-lymphocytes and an increase in the percentage of B-lymphocytes in the mid- and high-dose groups after 6 months of treatment. The *in vivo* clearance of *L. monocytogenes* was impaired in the high-dose group after 5 months of treatment. Treatment with tributyltin oxide did not induce a consistent effect on the natural killer cell activity of spleen and peritoneal cells after 4.5 months of exposure (decreased in the low- and high-dose groups, and increased in the mid-dose group). Based on the depression of IgE titers and increased *T. spiralis* in muscle after 5.5 months of exposure to tributyltin oxide, the study LOAEL is 0.25 mg/kg/day and the NOAEL is 0.025 mg/kg/day.

Dose and end point used for MRL derivation: 0.025 mg/kg/day; immunological effects.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Yes, conversions were done by the study authors.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure?
No

Other additional studies or pertinent information that lend support to this MRL: Numerous studies in animals have demonstrated that the main target for some alkyltin compounds, tributyltin among them, is the immune system, particularly the thymus (Boyer 1989; Seinen et al. 1977a, 1977b; Snoeij et al. 1985). Therefore, it is expected that additional intermediate-duration studies, which did not focus on the immune system, identified higher NOAELs. For example, a 4-week dietary study with tributyltin oxide in rats observed slight hematological abnormalities at 0.25 mg/kg/day and hepatic and body weight NOAELs at 1 mg/kg/day (Krajnc et al. 1984). That same study found a 17% in thymus weight at 1 mg/kg/day and a 35% decrease at 4 mg/kg/day. An additional study with tributyltin oxide reported reduced natural killer cell activity in rats at 1 mg/kg/day following 6 weeks of treatment (Van Loveren et al. 1990). In yet another rat study, Verdier et al. (1991) reported slight impairment in host resistance to *L. monocytogenes* following exposure to tributyltin oxide for 28 days at 5 mg/kg/day, but not at 1 mg/kg/day.

The NOAEL of 0.025 mg/kg/day of Vos et al. (1990) is supported by recent developmental studies with tributyltin chloride that evaluated systemic and immunologic parameters in the offspring of rats exposed to tributyltin chloride *in utero* (Gds 8-21), through the mother's milk, and directly as young adults until the age of 90 days (Cooke et al. 2004; Tryphonas et al. 2004). The doses tested were 0, 0.025, 0.25, and 2.5 mg/kg/day. Neither body weights nor food consumption was affected in the dams. No effects were observed on litter size, pup weight at birth, sex ratio, or survival until weaning. Growth of the treated pups after weaning was slightly reduced (<10%) relative to controls and analysis of food consumption and weight gain showed that male pups converted feed into weight gain less effectively than females. No effects were seen on the weights of pup's brain, kidney or adrenals, but there was a decrease in absolute and relative liver weight in 60-day-old females at 0.025 and 2.5 mg/kg/day, a decrease in absolute and relative liver weight in 90-day-old males at 2.5 mg/kg/day, decrease in absolute spleen weight in 30-day-old males at 2.5 mg/kg/day and in relative spleen weight in 60-day-old females at 2.5 mg/kg/day, and a decrease in relative thymus weight in 60-day-old females at 0.25 and 2.5 mg/kg/day and in absolute thymus weight in 30-day-old males at 2.5 mg/kg/day. No consistent treatment-related gross or microscopic lesions were observed in dams and pups. Clinical chemistry changes of potential biological importance included a decrease in serum amylase in 90-day-old males at 0.25 and 2.5 mg/kg/day and decreased T4, also in 90-day-old males at 2.5 mg/kg/day. Based on the changes in pup's organ weights and in clinical chemistry parameters, the 0.25 mg/kg/day dose is a LOAEL and 0.025 mg/kg/day a NOAEL. The reduced weight gain of the pups is not considered adverse because the difference with controls was less than 10%.

In the study of immunological parameters (Tryphonas et al. 2004), the only significant change in serum immunoglobulin levels that appeared dose-related was an increase in IgG at 0.25 and 2.5 mg/kg/day in 90-day-old males. Flow cytometric analysis of splenocytes showed a significant increase mean percent and absolute NK cell numbers in high-dose 30-day-old males and females, a decrease in the percentage,

but not in absolute numbers of CD4+8+ T cells in 60-day-old females, and an increase in the percentage of NK cells in 90-day-old males. The anti-SRBC IgM response was not affected by exposure to tributyltin. No significant alterations were observed in the lymphoproliferative activity of splenocytes in response to mitogen stimulation. The delayed-type hypersensitivity response (DTH) was not affected in 60-day-old females, but 90-day-old males showed a significant trend toward a decrease in DTH response with increasing doses of tributyltin. The assays for *L. monocytogenes* infectivity and NK cell activity did not give dose-related responses. Cytokine levels in serum were not affected. Gross examination of lymphoid tissues was unremarkable. The most consistent histological finding was mild to moderate cortical atrophy of the thymus, characterized by decreased numbers of cortical lymphocytes at 2.5 mg/kg/day at all ages.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Tributyltin oxide
CAS Number: 56-35-9
Date: April 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 79
Species: Rat

Minimal Risk Level: 0.0003 [X] mg/kg/day [ ] ppm

Reference: Vos JG, De Klerk A, Krajnc EI, et al. 1990. Immunotoxicity of bis(tri-*n*-butyltin)oxide in the rat: Effects on thymus-dependent immunity and on nonspecific resistance following long-term exposure in young versus aged rats. Toxicol Appl Pharmacol 105:144-155.

Experimental design: Groups of male Wistar rats were fed a diet containing 0, 0.5, 5, or 50 ppm tributyltin oxide (95.3% pure) for 18 months. This diet provided approximately 0, 0.025, 0.25, and 2.5 mg/kg/day of the test material. Parameters of specific resistance evaluated included IgM and IgG response to sheep red blood cells (SRBC) after 16 months; IgM and IgG response to ovalbumin and the delayed-type hypersensitivity (DTH) response to ovalbumin and tuberculin after 15 months of treatment; resistance to *T. spiralis* infection after 16.5 months; mitogenic response of thymus and spleen cells after 16.5 months; and surface marker analysis of mesenteric lymph nodes after 18 months. Parameters of nonspecific resistance examined included clearance of *L. monocytogenes* from the spleen after injection at 17 months and natural cell-mediated cytotoxicity of spleen and peritoneal cells after 16 months.

Effects noted in study and corresponding doses: No information was provided regarding body weight or weight of the thymus and spleen at termination. Exposure to tributyltin oxide did not affect the primary IgM or the secondary response to SRBC after 16 months of dosing. Neither the IgM nor IgG response to ovalbumin and *T. spiralis* were altered after 15 months of treatment, but the IgE responses to *T. spiralis*, as determined by the passive cutaneous anaphylaxis reaction, was suppressed in a dose-related manner (significant in the mid- and high-dose groups). The DTH reactions to ovalbumin and tuberculin were not significantly altered after 16 months of dosing. There was an increase in the number of larvae *T. spiralis* in muscle after infection in the mid- and high-dose groups after 16.5 months of exposure to the test material. No significant effect was observed on the response of spleen cells to T- and B-mitogens after 16 months. The cell surface marker analysis of mesenteric lymph node cells showed a reduction in the relative count of T-lymphocytes and an increase in the percentage of B-lymphocytes in the mid- and high-dose groups after 18 months of treatment. The *in vivo* clearance of *L. monocytogenes* was impaired in the high-dose group after 17 months of treatment. Treatment with tributyltin oxide for 16 months significantly reduced the natural killer cell activity of spleen and peritoneal cells, but there was no dose-response relationship. Based on the depression of IgE titers and increased *T. spiralis* in muscle after 16.5 months of exposure to tributyltin oxide, the study LOAEL is 0.25 mg/kg/day and the NOAEL is 0.025 mg/kg/day.

Dose and end point used for MRL derivation: 0.025 mg/kg/day; immunological effects.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
Yes, conversions were done by the study authors.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure?
No

Other additional studies or pertinent information that lend support to this MRL: The findings from the intermediate-duration portion of the Vos et al. (1990) study support the longer-term observations. A 2-year bioassay with tributyltin oxide in rats described hepatic, renal, endocrine, and body weight effects with a dose level of 2.1 mg/kg/day and NOAELs for these effects are approximately 0.2 mg/kg/day (Wester et al. 1990). In that study there also were changes in immunoglobulin levels at 2.1 mg/kg/day throughout the study, namely: increase in IgA after 12 and 24 months, decrease in IgG in females after 3 and 13 months, and increase in IgM after 3, 12, and 24 months. No additional chronic-duration studies were located for tributyltin oxide.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

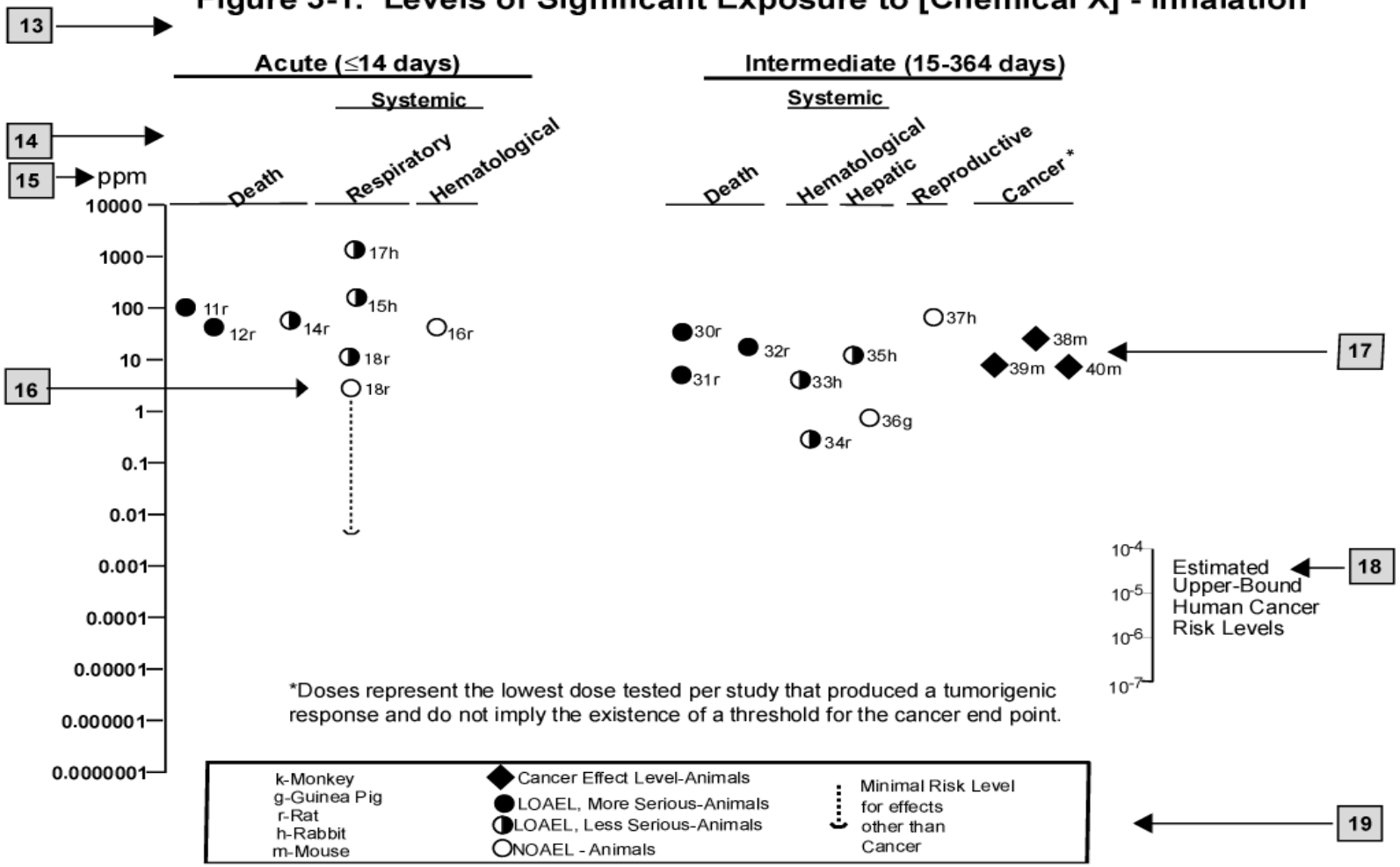
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

APPENDIX C

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

APPENDIX C

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX